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LIMITATIONS TO THE USE OF QUININE INTRAVENOUSLY IN THE TREATMENT OF MALARIA.[1]

By KENNETH F. MAXCY, Assistant Surgeon, United States Public Health Service.

Recently, along with the growing popularity of intravenous medication of various sorts, the intravenous injection of quinine has become a more common and widely used procedure in the treatment of malaria than formerly. *A priori*, the method appeals to one as being rational. It affords the opportunity of introducing the drug in known concentration directly into the blood stream in which the parasites are living. Theoretically it is the most exact and most effective mode of approach in the chemotherapy of malaria.

From the practical point of view, on the other hand, ever since the method was first advocated by Bacelli[2] it has been apparent to those who had large experience with the method that there were certain limitations to its field of usefulness. Without attempting a chronological review of the literature on the subject, it is the purpose of this paper to call attention again to certain dangers in the procedure and the precautions necessary in its use, with a view toward defining anew its proper field.

In judging the value of a method of treatment of malaria it is important to bear in mind that two objects are to be accomplished: First, the patient must be relieved of his acute attack; second, the parasites in his body must be damaged or destroyed to a degree that renders a relapse unlikely. While it is relatively easy to obtain data regarding the first requirement, it is rarely possible to follow up a sufficiently large series of treated cases over a sufficiently long period (at least six months and preferably a year or more) to establish the second point.

In this report attention is confined to the use of intravenous injection of quinine in the cure of the acute attack. The second point, i. e., the prevention of relapse, has been covered quite satisfactorily in recent war literature dealing with the treatment of thousands of cases of malaria among the soldiers returning from the Mediterranean war area. In these studies [3, 4, 5, 6] no evidence was obtained to indicate that the intravenous route of administration was more effective than ordinary mouth administration in the prevention of relapses. The questions formulated, then, are: What are the dangers in giving quinine intravenously? How can they be avoided? What are the clinical indications for the method?

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[1] From Field Investigations of Malaria, United States Public Health Service.
The author desires to acknowledge with thanks many courtesies extended by Surg. James K. Brew and the valuable laboratory assistance of Miss Cecelia Roberts.

[2] Bacelli: Gaz. degli. Osped., Feb. 1890. Riform med. 1890, *6*.

The dangers in giving quinine intravenously can best be illustrated by some observations made in a small series of cases in which this method was used without the safeguards that have been recommended, but with a technique that is not unusual in hospital and private practice. The plan of treatment was as follows: As soon as the diagnosis of malaria had been established, the patient was started upon a course of intravenous treatments *by routine.* The drug used was the double salt of quinine and urea hydrochloride. The preparation is marketed in solution in sterile ampules, 7½ grains each in 1 c.c. solution. The contents of two ampules (15 grains) was taken up in a 2 c.c. Luer syringe and injected into a vein at the bend of the elbow. This dose was repeated daily until from five to eight treatments had been given. The oral administration of the drug was then begun. The amount of this after-treatment varied within wide limits and was not looked upon as essential.

The results of this plan of treatment must be judged not only from the point of view of its effect upon the parasite in the blood stream, but also upon the patient himself. The ideal of chemotherapy is that the drug should be so administered as to "select and destroy the parasitic substance, *leaving unscathed the protoplasm of the host*".[7] The latter requirement is more important than the former in a simple uncomplicated case of malaria, in which the natural tendency is ordinarily toward spontaneous cure. Quinine injected intraveneously into man may manifest quite definite effects upon the circulatory system, the nervous system, and upon the skin and subcutaneous tissues when these are involved at the site of injection.

A. EFFECT UPON PATIENT.

1. *Circulatory system.*—It has long been known that quinine is a circulatory depressant. In this connection it is interesting to note that the closely related alkaloid, quinidine (the dextro-rotatory, stereoisomer of quinine) has recently received considerable attention in

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[3] Mayne, Bruce, and Moss, M. M.: Abstracts of the studies which were made at the request of the British War Office. Reprint No. 629 from Pub. Health Rpts., Dec. 24, 1920, pp. 3082–3091.

[4] Zweig and Matko: Wien. klin. Wchnschr., *29*, 1916, pp. 1516–1522.

[5] Hehir, P.: Ind. Jour. Med. Res. (Sp. Ind. Sci. Number) 1919, pp. 89–100.

[6] Acton, Hugh W. et al.: Ind. Jour. Med. Res., *8* (Apr.) 1921, pp. 750–871.

[7] Editorial, "Recent Tendencies in Chemotherapy," Jour. Am. Med. Assn., *77*, Nov. 19, 1921, p. 1658.

the treatment of auricular fibrillation [8, 9, 10] and hypertonia. Quinidine has been shown to cause a fall in blood pressure when injected intravenously into dogs.[11] McCarrison and Cornwall [12] have shown that all salts of quinine produce a profound fall in blood pressure after intravenous injection in sheep. Finally, Brahmachari [13] has observed a fall in blood pressure following rapid intravenous injection of concentrated solutions of quinine in man in the treatment of malaria.

Our own observations confirm those of Brahmachari. Blood pressure and pulse rate were determined before and at frequent intervals following the intravenous injection of quinine and urea hydrochloride (15 grains in 2 c. c. suspension) in a series of cases under treatment for malaria. It was found that when the time taken for the injection was short, a marked effect upon pulse rate and blood pressure was almost sure to result. Before the syringe was completely emptied, the pulse rate began to pick up. It became rapid and weak and sometimes slightly irregular. The disturbance in heart action seemed to reach its maximum in something less than two minutes. The number of beats per minute sometimes increases to 125 or more. Recovery was usually rapid, the rate coming back to normal in 5 to 15 minutes.

Along with this disturbance in heart action there was a decided drop in blood pressure which was apt to be maintained for some time after the pulse rate had come back to normal. The systolic pressure often dropped 10 to 20 mm. Hg., and the diastolic from 5 to 10 mm. Hg. Maximum effect was usually noted in two to three minutes. It was often an hour or more before the former level was reached.

The following observations are given as illustrative examples:

CASE J. D.

Diagnosis: Malaria, tertian, chronic, and acute. Enlarged spleen.

Sept. 22.—Second injection; given in 15 seconds. Pulse rose from 72 to 92; back to normal in 5 minutes. Blood pressure fell from 100/70 to 92/70; normal reading obtained after 1½ hours.

Sept. 23.—Third injection; given in 15 seconds. Pulse rose from 68 to 92; normal in 5 minutes. Blood pressure fell from 95/65 to 90/60; rose to previous level in 15 minutes.

Sept. 24.—Fourth injection; given in 25 seconds. Pulse rose from 68 to 92; normal in 5 minutes. Blood pressure dropped from 100/65 to 95/65; reached former level in 30 minutes.

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[8] Frey, W.: Berl. klin. Wchnschr., *55*, 1918, pp. 417-451.

[9] Levy, Robert L.: Jour. Am. Med. Assn., *76*, 1921, pp. 1289-1293. (*See also* Editorial, Jour. Am. Med. Assn. *77*, 1921, p. 1822.)

[10] Cheinisse, L.: Presse med., Paris, *29*, 1921, p. 748.

[11] Cohn and Levy: Proc. Soc. Exp. Biol. and Med., *18*, 1921, p. 283.

[12] McCarrison, R. and Cornwall, J. W.: Ind. Jour. Med. Res., (Jan.) 1919, pp. 248-261.

[13] Brahmachari, U. N.: Lancet, II, 1920, pp. 1301-1302.

Sept. 25.—Fifth injection; given in 10 seconds. Pulse rose from 70 to 100; normal in 5 minutes. Blood pressure fell from 100/70 to 85/65; reached former level in 15 minutes.

CASE B. M'C.

Diagnosis: Malaria, tertian, chronic, and acute. Enlarged spleen.

Sept. 22.—First injection; given in 25 seconds. Pulse rose from 68 to 80. Blood pressure fell from 120/75 to 110/70; back to normal in 1 hour.

Sept. 23.—Second injection; given in 30 seconds. Pulse 88; no acceleration. Blood pressure fell from 120/80 to 110/65; back to normal in 30 minutes.

Sept. 24.—Third injection; given in 15 seconds. Pulse rose from 68 to 92. Blood pressure fell from 110/70 to 100/65; back to normal in 1 hour.

CASE A. B.

Diagnosis: Malaria, tertian, acute. Enlarged spleen.

Sept. 28.—First injection; given in 30 seconds. Pulse rose from 90 to 112. Blood pressure fell from 115/65 to 110/70; back to normal in 5 minutes.

Sept. 29.—Second injection; given in 15 seconds. Pulse rose from 100 to 120. Blood pressure fell from 110/75 to 100/65; back to normal in 5 minutes.

Sept. 30.—Third injection; given in 60 seconds. Pulse rose from 72 to 100. Blood pressure fell from 110/75 to 108/65; back to normal in 5 minutes.

CASE A. R.

Diagnosis: Malaria, aestivo-autumnal, acute. Enlarged spleen.

Sept. 30.—Second injection; given in 60 seconds. Pulse rose from 100 to 140; was recorded at 80 from 5 to 15 minutes after, and rose to 100 again in 30 minutes. Blood pressure fell from 125/75 to 105/75; reached former level in 1 hour.

Experimental and clinical observations thus agree that the rapid intravenous injection of a concentrated solution of quinine may have a pronounced depressing effect upon the circulation. The possibility of producing this effect upon the patient who is being treated for malaria must be considered carefully. If the patient is already suffering from circulatory embarrassment or the severe hypotonia sometimes associated with chronic aestivo-autumnal infections, the added burden produced by the well-intended therapeutic effort may result in a fatal outcome instead of improvement.

2. *Central nervous system.*—Whether the subjective symptoms of acute cinchonism are to be attributed to a direct action on nervous tissue or are more or less dependent upon circulatory changes is not altogether clear. However, that the drug has an affinity for nervous tissue is demonstrated in its action on the retina (toxic amblyopia), on the auditory ganglia (toxic deafness), and on peripheral nerves (paralysis following intramuscular injections).

Subjective symptoms of acute cinchonism of a more or less severe degree invariably follow intravenous injections of the type described above. The severity of the reaction is in a general way proportional to the speed with which the injection is made, but the well-known factor of individual idiosyncrasy comes into play. In the usual run of cases, the reaction is disagreeable to the patient, but not alarming. Following the emptying of the syringe, he complains of a bitter taste, ringing in his ears, blurring of vision, and a queer, confused, dizzy feeling. In a few cases in which the injection was very rapid, an alarming reaction was observed. Besides the symptoms noted above, the patient broke into a profuse sweat, his pupils became dilated, his expression became fixed and staring, the facial muscles twitched, and a convulsion seemed imminent. The condition, however, usually reached its worst in 3 to 10 minutes and then gradually subsided. It was not unusual, however, for an hour or two to elapse before the patient really "felt himself" again.

Of 11 instances on which notes were made the reaction was practically negligible in 3, moderate in 6, and very severe in 2.

Along with these nervous manifestations attending the rapid injection of concentrated solutions of quinine, which may be extremely disagreeable to the patient, the possibility and danger of encountering a patient with a violent individual idiosyncrasy to the drug must be constantly borne in mind.

3. *The skin and subcutaneous tissues.*—Attention to the destruction wrought upon the tissues by concentrated solutions of quinine has been brought by a number of observers in discussing the relative advantages and disadvantages of intramuscular and subcutaneous injections. The subject has been treated experimentally in a very complete way by Dudgeon.[14] It suffices to say that the necrotizing action of concentrated solutions of quinine upon tissues is comparable to that of salvarsan and all of the precautions guarding against extravasation around the point of injection of the latter drug should be observed in injecting quinine. An accident of this nature is almost sure to be followed by swelling, pain, loss of motion, and, finally, necrosis with sloughing and a resultant wound which is extremely slow to heal. Occasionally thrombosis of a vein and paralysis of a peripheral nerve by direct involvement has been known to occur.

In the series of cases reported by the British War Office (see ref. footnote 3) of 127 injections of quinine bihydrochloride (15 grains) in 8 patients, thrombosis occurred in 4 patients, 2 in both arms and 2 in one arm only. In the small series of cases upon which this report is based, the following four accidents of a similar nature came under observation.

Case No. 9.—Diagnosis: Malaria, simple tertian. Admitted to the hospital in July. Given a series of five intravenous injections. Readmitted to the hosital two months later with a relapse. The patient was found to have an area about 3 inches long and 2 inches wide on the external aspect of his left lower fore arm, which was anesthetic to epicritic sensation. He stated that this had resulted from the intravenous treatments previously given.

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[14] Dudgeon, Leonard S.: Jour. of Hyg., *18*, 1919, p. 317.

Case. No. 2.—Diagnosis: Malaria, simple tertian. Admitted to the hospital in September. A small amount of solution extravasated during the fourth injection. The arm became swollen and painful at the bend of the elbow. Skin did not break down, but normal contour and motion were not restored until several days later.

Case No. 3 (A. R.).—Diagnosis: Malaria, aestivo-autumnal. Admitted to hospital September 22. On October 17 small amount of quinine solution extravasated during injection. Skin and subcutaneous tissues subsequently broke down and sloughed, leaving a punched-out area the size of a hickory nut, which healed very slowly.

Case No. 13.—Diagnosis: Malaria, simple tertian. Admitted to hospital September 9. Given four intravenous injections and discharged on September 17. Readmitted September-22 with suppurating wounds at the bends of both elbows. These healed very slowly and were not completely closed over when he was discharged on October 15.

Experiences of this sort, which may happen to anyone with ordinary skill in giving intravenous injections, counsel conservatism in using the method in the usual run of malarial infections.

From the above considerations, it is evident that the method does not always achieve the ideal laid down for chemotherapy of "leaving unscathed the protoplasm of the host."

B. ACTION ON PARASITES.

1. *Asexual forms (ring forms) in the peripheral blood.*—The specific action of quinine upon the asexual (ring) forms in the peripheral blood is effected quickly and surley by intravenous administration. Its action in this regard is probably more rapid [15] than when given by either of the other routes—oral or intramuscular.

In the series of cases observed in this study, ring forms were seldom found after the first injection. In only two instances did they persist until after the second had been given. It must be admitted, however, that in an equal number of cases treated by oral administration of 30 grains daily, practically the same result was obtained. The superiority of one method over the other in this regard is therefore not especially notable; but where time is an important factor in instituting the treatment of a given case, the intravenous mode of administration has an obvious advantage. Its efficacy in curing the average acute attack is undoubted.[16] [17] [18]

2. *Sexual forms (crescents) in the peripheral blood.*—There still seems to be a reasonable doubt in the mind of most observers whether quinine has a direct action on crescents. It was not surprising then to find in at least two cases which came under our observation that

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[15] James, S. P.: Trop. Dis. Bull., *13*, 1919, p. 92.

[16] Patrick, Adam: Jour. R. A. M. C., *32*,1919, pp. 295–301.

[17] Pitt, G. Newton: Guys Hosp. Reports, *71*, 1921, pp. 21–25.

[18] Woodcock, H. M.: Jour. R. A. M. C., *34*, 1920, pp. 385–396.

the intravenous injection of the drug apparently had no more effect upon crescents than did the oral administration.

Case No. 3 (A. R.)—Admitted September 22. Diagnosis: Malaria, aestivo-autumnal. Blood smears showed large numbers of rings and crescents. Given quinine sulphate gr. 30 daily by mouth for one week. Ring forms disappeared on the second day, but the crescents were undiminished in numbers. He was then given a series of seven intravenous injections of quinine and urea hydrochloride, 15 gr. each. Smears still showed large numbers of crescents. Treatment was continued by mouth, 30 grains of the sulphate daily until November 4 (sixth week of treatment), when the first negative smear was obtained. He was discharged on 10 grains daily.

Case No. 12 (J. L.)—Admitted September 13. Diagnosis: Malaria, aestivo-autumnal. Blood smears showed large numbers of rings and crescents. He was given a series of six intravenous injections and was discharged. Took no after treatment. Readmitted to the hospital on October 14 (same year) with a severe relapse, presenting marked gastro-intestinal symptoms. Given four intravenous injections and then the treatment was continued by mouth, 40 grains daily. Crescents were still present on November 1, but a negative smear was reported on November 5 (end of third week).

From these instances and the literature at present available, it seems reasonable to conclude that the intravenous route of administration possesses no advantages *per se* over ordinary mouth administration in ridding the peripheral blood of crescents.

DISCUSSION.

When quinine is given intravenously by routine in the treatment of malaria, as outlined above, it can hardly be claimed that the procedure is without danger of untoward result. The sudden introduction of a concentrated solution into the blood stream tends to cause circulatory depression and distressing nervous phenomena. Whenever accidental extravasation into the tissues at the point of injection occurs, local necrosis and sloughing is apt to result.

To be weighed against these dangers to the patient, is the unquestionable rapidity with which the drug is brought into contact with the parasites in the blood stream. Except with regard to this advantage, viz, the rapidity with which therapeutic control may be initiated by this route, there is no clear evidence at present that it is more effective in the ordinary run of malarial infections than is mouth administration of the drug in curing the acute attack, in ridding the blood of sexual forms, or in preventing relapse.

Its proper field of usefulness would seem to be upon urgent clinical indications of two sorts. First, it is the method to be used in those cases of malaria in which prompt absorption by the gastro-intestinal tract, following mouth administration, is not to be expected, on account of violent gastro-intestinal disturbance or other cause, or in which it is impossible to give the drug by mouth on account of the mental condition of the patient, i. e., delirium, coma, etc. Secondly, it is the method to be used in those cases of malaria which are gravely ill when first seen by the physician and in whom it is deemed imperative to secure immediate cinchonization. It does not seem necessary nor desirable to use the intravenous route of administration in the simple acute or chronic infections ordinarily encountered, whether tertian or aestivo-autumnal, on account of the added risk and discomfort to the patient.

In those cases in which the clinician decides that the use of the method is warranted, the effect of the drug upon the patient must be borne in mind. Particularly is it necessary to be sure that the patient is not suffering from circulatory embarrassment before the injection is undertaken. The technique of the injection must be such as to minimize the danger of untoward effects. This may best be secured by observing three cardinal principles:

A. Careful *aseptic technique.*
B. Giving the drug in moderate doses and *in dilution.*
C. Introducing the solution into the blood stream *slowly.*

It has been demonstrated to our own satisfaction now in a considerable series of cases that when these precautions are observed, the average patient experiences little or no discomfort and there is little, if any, noticeable effect upon the circulation.

All the precautions which are observed in giving a dose of salvarsan should be observed in giving quinine. A sterile filtered solution of the quinine salt (di-hydrochloride is generally recommended) should be prepared and diluted so that 1 c. c. contains not more than ½ grain of the drug. The size of the dose should not exceed 15 grains for a normal adult (see ref. footnote 3). It is advisable to start with a dose of 5 grains and increase to 10 or 12 grains in the subsequent injections. The solution containing the proper amount of the drug may be taken up in a 25 c. c. syringe and injected very slowly at the rate of about 1 c. c. per minute. The injection should be discontinued immediately if there is any suspicion that the solution is not going into the vein properly. Extra care should of course be given in the case of individuals who claim an idiosyncrasy for the drug.

Where there is thought to be danger of circulatory collapse, it is advisable to make frequent readings with the blood pressure apparatus during and for several hours after the injection. The therapeutic action of adrenalin is antagonistic to that of quinine and should be used to combat the depressing effect which the quinine salt may have upon the circulation.

The intravenous administration of quinine should be discontinued as soon as the clinical indications which rendered its use advisable have subsided and cinchonization continued by mouth administration until the acute attack is relieved. The eight weeks or more of after treatment necessary for sterilization of the patient's blood should always follow.

CONCLUSIONS.

1. The dangers in the intravenous injection of quinine in the treatment of malaria are: Depression of the circulation; disagreeable and alarming nervous phenomena; and local necrosis and sloughing at the point of injection.

2. No evidence is found to indicate that this route possesses special advantages over ordinary mouth administration of the drug in curing the acute attack or in ridding the blood stream of sexual forms (crescents), except with regard to the speed with which therapeutic control may be initiated.

3. The method should be reserved for those cases with urgent clinical indications or in which mouth administration of the drug is impracticable for any reason.

4. The untoward effects which may result from intravenous administration of quinine may be largely avoided by rigorously observing certain precautions similar to those found necessary in the injection of such drugs as salvarsan.

CASES OF INFLUENZA REPORTED BY STATES, 1922.

The accompanying table shows, by weeks, the number of cases of influenza reported by State health officers from January 22 to March 18, 1922.

On pages 640-641 of the Public Health Reports for March 17, 1922, appears a table giving the number of cases of influenza reported by State health officers during the first 10 weeks of the years 1920, 1921, and 1922.

The aggregate estimated population of the 28 States and the District of Columbia is approximately 67,200,000.

Number of cases of influenza reported by States from Jan. 22 to Mar. 18, 1922, inclusive, by weeks.

State.	Number of cases reported during week ended—							
	January.	February—				March—		
	28	4	11	18	25	4	11	18
Alabama	3	26	95	29	20	31	185	340
Arkansas	88	192	232	158	202	371	409	529
California	48	92	845	4,315	10,033	9,917	4,627	3,289
Colorado (exclusive of Denver)	2	4	6	17	12	67	937	755
Connecticut	22	109	518	1,325	675	711	486	194
Delaware	2	7	2	2	9	....	2	16
District of Columbia	7	5	9	8	7	9	9	3
Florida	6	15	35	123	118	68	72	74
Georgia	64	74	81	128	162	179	149	268
Illinois	125	108	417	633	1,069	809	735	765